Glomerular Filtration Rate, Renal Blood Flow and Blood Viscosity during and after Diabetic Coma

By François C. Reubi, M.D.

The azotemia of patients in diabetic coma is the result of impaired blood supply, unless tubular impairment antedates or supervenes. Clearance and blood pressure data are presented which strongly suggest that increased blood viscosity is the dominant reason for the reduced renal blood flow.

It has long been recognized that renal disturbances may develop during the course of a diabetic coma. But only a few attempts have been made to evaluate the nature and the cause of these changes. In a first approach to this problem, McCance and Widdowson found a decreased inulin clearance and low creatinine/inulin and urea/inulin clearance ratios. Two years ago, we reported a case in which the decrease in renal blood flow occurring during coma was directly proportional to the increase in blood viscosity. In a subsequent paper, these results were confirmed and observations extended to six other cases. More recently, a paper dealing with similar investigations has been published by Bernstein and co-workers; the authors did not, however, determine the renal extraction of para-aminobenzoic acid, nor did they attempt to evaluate the role of the blood viscosity in their six subjects. The purpose of the present article is to summarize previous results and to report additional data on this problem.

Methods

Eight patients were submitted to various clearance procedures during diabetic coma and several days after the acute acidotic episode had been controlled. In an additional patient (number 9), the clearance determinations were performed only once, since this subject died shortly afterwards from diabetic acidosis and hypokalemia.

Glomerular filtration rate was estimated from the sodium thiosulfate clearance and effective renal plasma flow from the PAH (para-aminobenzoic acid) clearance, using the infusion technique recommended by Goldring and Chasis. Urea was analyzed by the method of Conway. In the subject who died, and in three diabetics of the first group, renal extraction of PAH was also measured in the acute stage by catheterization of the right renal vein, using the technique devised by Courand and Ranges, and modified by Warren and colleagues. True renal blood flow was calculated by the formula:

\[
RBF = \frac{C_{PAH}}{E_{PAH}(1 - H_c)}
\]

in which RBF = true renal blood flow; \( C_{PAH} \) = PAH clearance; \( E_{PAH} \) = renal extraction of PAH; and \( H_c \) = hematocrit.

The renal extraction of PAH was assumed to be unchanged after recovery from the coma. In all cases of the first group in which it had not been measured, it was considered to be normal, that is, 0.92 ± 0.04.

Effective blood viscosity was estimated using Lamport's formulae and charts, which required determination of hematocrit readings and plasma protein concentrations. These two variables were determined in every case during and after coma.

The blood pressure was measured in the arm by the auscultatory technic.

According to Lamport,

\[
\text{Resistance} = \frac{\text{Perfusion pressure} - \text{"yield pressure"}}{\text{Rate of flow} \times \text{viscosity}}
\]

In our cases, the blood pressure remained essentially unchanged during and after the acidotic episode. The changes in "yield pressure" probably also can be neglected. If this assumption is true,

\[
\text{Renal arteriolar resistance} = \frac{\text{Constant}}{\text{Renal blood flow} \times \text{viscosity}}
\]
That means that, if the product (renal blood flow \( \times \) viscosity) remains constant during and after coma, no change in renal vascular resistance has taken place during diabetic acidosis. This product was calculated in all our cases.

**Results**

In subjects 1 through 8, (table 1), there was a sharp reduction of urea clearance, glomerular filtration rate, and PAH clearance during diabetic coma. The filtration fraction was not consistently altered, being sometimes below and sometimes above the control value. The ratio \( C_U/C_T \) usually increased. Nonprotein nitrogen rose significantly. Renal extraction of PAH, measured in three subjects, was normal in one, and only slightly reduced in the other two. Hematocrit readings and plasma protein concentrations were much higher during coma than after recovery, so that blood viscosity increased. Renal plasma flow was affected more than true renal blood flow, owing to the marked hemococoncentration. Blood pressure remained essentially normal, except in patient 8, who showed mild hypertension.

All control values, that is, values obtained after recovery from the acidosis, were practically normal, except for the blood pressure and \( C_{PAH} \) in patient 8, who may have had some degree of pre-existing renal impairment (nephronephrosis).

The values obtained by multiplying blood viscosity by true renal blood flow, \( (V \times RBF) \) were of the same order of magnitude during and after coma for each patient. The quotient \( \frac{V \times RBF \text{ (coma)}}{V \times RBF \text{ (recovery)}} \) varied between 1.11 and 0.80, with an average of 1.01, indicating that renal arteriolar resistance remained practically identical during and after coma.

**Table 1.** Relationship Between Blood Viscosity and Renal Functions in Diabetic Subjects during and after Coma

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Stage</th>
<th>B.P. mm. Hg</th>
<th>N.P.N. mg. %</th>
<th>Hema-</th>
<th>Plasma Proteins Gm.</th>
<th>Blood Viscosity (cst)</th>
<th>( C_U ) cc. / min.</th>
<th>( C_T ) cc. / min.</th>
<th>( C_{PAH} ) cc. / min.</th>
<th>( F_F )</th>
<th>( R_BF ) cc. / min.</th>
<th>( R_BF \times \times )</th>
<th>Product ( R_BF \times \times )</th>
<th>Quotient ( \frac{R_BF \times \times \text{ (coma)}}{R_BF \times \times \text{ (recovery)}} )</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Coma</td>
<td>120/60</td>
<td>56.5</td>
<td>12.0</td>
<td>6.6</td>
<td>48</td>
<td>24</td>
<td>229</td>
<td>0.81</td>
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<td>540</td>
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<td>19.3</td>
<td>10.6</td>
<td>5.8</td>
<td>63</td>
<td>43</td>
<td>245</td>
<td>0.68</td>
<td>0.26</td>
<td>0.26</td>
<td>490</td>
<td>3550</td>
<td>1.01</td>
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<td>19.2</td>
<td>7.3</td>
<td>3.6</td>
<td>110</td>
<td>71.5</td>
<td>500</td>
<td>0.55</td>
<td>0.22</td>
<td>0.22</td>
<td>780</td>
<td>2510</td>
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<td>5.0</td>
<td>60</td>
<td>63</td>
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<td>0.77</td>
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<td>0.29</td>
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<td>28.3</td>
<td>8.0</td>
<td>3.9</td>
<td>108</td>
<td>73</td>
<td>540</td>
<td>0.64</td>
<td>0.20</td>
<td>0.20</td>
<td>770</td>
<td>2170</td>
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<td>66.5</td>
<td>12.1</td>
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<td>156</td>
<td>166</td>
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<td>54.5</td>
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<td>75</td>
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<td>4.0</td>
<td>124</td>
<td>76</td>
<td>510</td>
<td>0.61</td>
<td>0.24</td>
<td>0.24</td>
<td>1100</td>
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<tr>
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<td>100/70</td>
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<td>10.4</td>
<td>5.4</td>
<td>54</td>
<td>188</td>
<td>640</td>
<td>0.67</td>
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<td>59</td>
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<td>55.3</td>
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<td>4.6</td>
<td>36</td>
<td>39</td>
<td>125</td>
<td>0.48</td>
<td>0.30</td>
<td>0.30</td>
<td>520</td>
<td>2390</td>
<td>1.09</td>
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</table>

* Signifies blood urea nitrogen determinants made.
tufts and in the peritubular capillaries throughout the kidney. The anatomic diagnosis was acute degenerative tubular nephropathy.

**DISCUSSION**

From the data presented, it seems likely that the azotemia occurring in diabetic coma is chiefly due to renal disturbances. During coma, there is a marked reduction in renal blood flow, renal plasma flow, glomerular filtration rate, and urea clearance, which may account for the observed rise in nonprotein nitrogen or blood urea nitrogen. However, increased production of urea, due to protein breakdown, might be partly responsible.

In most patients, however, the renal changes are only transitory, and in cases 1 to 8, renal function was restored to normal values as soon as acidosis had subsided. True renal ischemia seems to be associated with diabetic coma. Renal extraction of PAH was measured in cases 1, 7, and 8, and found to be normal or only slightly reduced, so that the PAH clearance probably allows a reliable estimation of the kidney circulation in most cases. This ischemia could be due to decreased cardiac output, active renal arteriolar constriction, or increased blood viscosity. But cardiac output has been shown by Howarth and colleagues to be somewhat increased in this condition. By applying the above-mentioned formulas, it was found that no vasoconstriction occurs during the stage of acidosis. We believe, therefore, that increased blood viscosity alone, due to severe dehydration, may account for the observed slowing down of the kidney circulation. In all cases of the first group (1 to 8), improvement of the renal function occurred promptly, as soon as blood viscosity had returned to normal values, which was readily achieved by parenteral fluid and insulin therapy. Glomerular changes are absent at the autopsy of such patients, unless they had pre-existing lesions (diabetic glomerulosclerosis or vascular nephrosclerosis). Organic tubular alterations, which may develop in severe cases, such as patient 9, can almost be ruled out in patients 1 through 8, because of the rapid improvement in renal clearances following rehydration and the nearly normal PAH extraction in cases 1, 7, and 8. The renal inefficiency in these cases was a consequence of a pure "functional nephropathy."

It is interesting to note the different behaviors of the renal vascular tree in conditions of acutely and chronically increased viscosity. It seems to remain quite passive in acute diabetic coma, but in polycythemia vera, in which chronic hyperviscosity excels, total renal blood flow is usually increased, which means that a compensatory drop in arteriolar resistance takes place. No such hemodynamic compensation can be observed in diabetic acidosis.

In contrast to the functional type of renal failure, organic tubular lesions were found only in patient 9. Their existence was strongly suggested before death by the low extraction ratio for PAH (0.48) and the high urea/thiosulfate clearance ratio. Decreased renal PAH extraction might also have been brought about by the opening of a shunt; but histologic examination, showing clearly the tubular alterations, failed to reveal cortical ischemia and/or medullary hyperemia; the blood was uniformly distributed throughout the kidney. In this case, we may assume that not only the excretion of PAH was impaired, indicating a lesion of the proximal tubules, but also that some thiosulfate was diffusing back through the damaged tubular membranes, accounting for the high urea/thiosulfate ratio.

The cause of this type of organic nephropathy is unknown. Several factors may play a role, for instance, ischemia and electrolytic disturbances which lead to acidosis and hypokalemia. In our case, ischemia as well as hypokalemia were presumably involved.

**SUMMARY**

Renal functions were studied in nine patients during and after diabetic coma, by means of the clearance methods. In four cases renal extraction of PAH was determined by catheterization of the right renal vein. All patients showed a sharp reduction of urea clearance, glomerular filtration rate, effective renal plasma flow, and true renal
blood flow at the time of coma. The blood viscosity was markedly increased. Moderate azotemia was present.

In eight patients, the disturbed renal functions were promptly restored to normal values after correction of the dehydration. In three of them, renal extraction of PAH was found to be normal, or slightly below normal values, during coma. The slowing down of the renal circulation, which accounts for the azotemia in these eight cases, appears to be due to increased blood viscosity, for the product (renal blood flow × viscosity) remained constant during and after coma. This condition may be called “functional nephropathy.”

In the ninth patient, who died from diabetic acidosis and hypokaliemia, we found a decreased renal extraction of PAH, suggesting tubular impairment. Postmortem examination revealed granular and fatty degeneration of the proximal convoluted tubules. We attribute this organic tubular nephropathy partly to renal ischemia, partly to electrolytic disturbances.

REFERENCES

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FRANÇOIS C. REUBI

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